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(71)(72) Applicant and Inventor: LANE, L. William (US/US); 206 Main Street, #11, Milburn, NJ 07041 (US). (74) Agents: RODMAN, Charles, B. et al.; Rodman & Rodman, 7-11 South Broadway, White Plains, NY 10601 (US).	
(54) Title: PROCESSING SHARK CARTILAGE	
(57) Abstract <p>In the low temperature processing of natural shark cartilage into a substantially 100 % pure finely divided state, the cartilage is separated from any residual shark tissue, then chopped into particles of about 1/4 inch and dried. The dried shark cartilage is then further reduced in particle size to about 100 to 325 mesh. Thereafter, a conditioning step is used to germinate any bacterial spores present in the shark cartilage. The conditioned shark cartilage, with the bacteria germinated during the conditioning step is then exposed to a sterilizing gas to destroy substantially all of the activated germinated bacteria under low temperature conditions which do not degrade the inherent nutritional content or denature the potency of the protein activity of the natural shark cartilage.</p>	

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PROCESSING SHARK CARTILAGE**Background of the Invention****Field of the Invention**

5 This invention relates to the low temperature processing of shark cartilage from its natural state into a substantially pure, finely divided state for use as a nutritional and health supplement, and more specifically, to an improved process for producing substantially 100% pure shark cartilage without denaturing the potency of the protein and
10 mucopolysaccharide factors, or degrading the inherent nutritional content of the shark cartilage in its natural state.

The Prior Art

15 Skeletons of sharks are made of pure cartilage, a hard gristly material formed from rod-like protein fibers, complex carbohydrates and minerals, principally calcium and phosphorus. Less dense and more pliable than bone, cartilage enables the shark to be buoyant and flexible.

20 Bone is composed primarily of calcium, phosphorus and other minerals, whereas pure shark cartilage usually contains substantially smaller amounts of these components. Cartilage does not contain blood vessels or nerves, whereas bone does. Cartilage also does not contain the microscopic canals that

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bone has to permit the passage of blood vessels and nerve fibers.

About 6-8% of a shark's gross weight is cartilage. In contrast, only a small fraction of 1% of a mammal's gross weight is cartilage. In humans, for example, cartilage is found in the harder parts of the ears and nose, around joints, at the ends of long bones, and between the segments of the spine. In an average calf, a mammal whose weight is roughly equivalent to that of an average shark, cartilage constitutes only about 0.06% of the total body weight. In comparison, a shark has about 100 times as much cartilage as a calf or other similar sized mammal.

In addition to sharks having a higher percentage of cartilage than mammals, shark cartilage is also different because it has some calcification. Shark cartilage is reinforced at stress points with plates of apatite, a substance composed of calcium phosphate and carbonates.

In processing shark cartilage from its natural state into a pure, dry and finely divided state, operations such as drying, pulverization and sterilization are needed and can employ excessive heat, which adversely effects important properties of the shark cartilage. In addition, treatments that utilize solvents or chemicals can denature the active protein factor in the shark cartilage and thus render the shark cartilage therapeutically valueless. Proteins are easily

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denatur d by heat and by various chemicals such a solvents and acids that ar oft n used to remove fats and other unwanted components.

In order for a human or animal recipient to obtain the nutritional and therapeutic benefits of shark cartilage in an efficacious manner, the shark cartilage should be in the form of finely divided particles. In this way, it can be absorbed into the body of the human or animal recipient as quickly as possible, to prevent the protein from being digested by proteolytic enzymes. If digested by these enzymes, the protein content of the shark cartilage is broken down into its constituent amino acids which are not effective in angiogenesis inhibition.

The shark cartilage therefore must be sufficiently finely divided in order to be absorbed into the system of the human or animal recipient as a suspension of preformed protein as quickly as possible. This is easier said than done, because shark cartilage in its natural state is a tough, gristly, elastic material, containing about 75 to 85 weight % moisture and is difficult to convert into finely divided particles.

U.S. Patent No. 5,075,112 to Lane discloses a method of, and dosage units for inhibiting angiogenesis or vascularization by means of administering to an animal or human host an effective amount of shark cartilage, in the form of finely divided powder, tablets, capsules or suppositories.

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The efficacy of the shark cartilage for use as an anti-angiogenic substance to prevent vascularization is determined by those skilled in the art by means of a technique called the Chicken Chorioallantoic Membrane (CAM) assay. The CAM assay is discussed in detail in the aforementioned U.S. Patent No. 5,075,112 to Lane, particularly at columns 3 to 6.

Briefly, in a CAM assay, the development of new blood vessels is measured in a chicken embryo. The extent of new vascularization is given a numerical rating, called the Vascularization Index (VI). The VI is determined from a low power microscope assessment of the possible changes in the CAM vascularization. The amount of microscopic field where vascularization is inhibited, and the degree of inhibition are estimated and given the VI numerical rating or score. A VI rating of 2.0 is a perfect score and indicates the absence of capillaries and other small blood vessels. A VI score of 1 indicates significantly reduced vascularity. A VI score of 0 shows no change in density or number of blood vessels, and is an indication of no activity.

A CAM activity range of about 0.85 to 1.1 is considered effective angiogenesis inhibition. The potency of shark cartilage as an angiogenesis inhibitor is believed to be directly related to the potency of its active protein factor.

It is an objective of this invention to preserve the nutritional and biological integrity of the natural shark

cartilage during its processing into a finely divided product for human or animal consumption.

SUMMARY OF THE INVENTION

In the low temperature processing of natural shark cartilage into a substantially 100% pure finely divided state, the cartilage is separated from any residual shark tissue, then chopped into particles of about $\frac{1}{4}$ inch and dried. The dried shark cartilage is then further reduced in particle size to about 100 to 325 mesh. Thereafter, a conditioning step is used to germinate any bacterial spores present in the shark cartilage. The conditioned shark cartilage, with the bacteria germinated during the conditioning step is then exposed to a sterilizing gas to destroy substantially all of the activated germinated bacteria under low temperature conditions which do not degrade the inherent nutritional content or denature the potency of the protein activity of the natural shark cartilage.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In addition to the inherent nutritional benefit of shark cartilage, it is believed that two factors are also important in producing the beneficial health effects attributed to shark cartilage. One factor is the carbohydrate or mucopolysaccharide content of the shark cartilage which is believed to stimulate the immune system of the body to resist and fight disease. The second important factor is the anti-

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angiogenic factor found in the protein portion, which can contain as many as five different active proteins.

5 The effectiveness of the protein and mucopolysaccharide content can be easily destroyed by improper processing and handling of the shark cartilage, especially at high temperatures, above about 150°F.

10 Whole shark cartilage contains about 30-40 weight % total protein which is believed responsible for the inhibition of angiogenesis, and about 6.0-9.0 weight % carbohydrate which contains the mucopolysaccharide portion which is believed to stimulate the immune system to fight disease. The fat content of shark cartilage is less than about 0.3 weight %. Mineral content comprises at least about 50 weight % of the total shark cartilage of which about 20 weight % of the total shark cartilage is calcium and about 10 weight % of the total shark cartilage is phosphorus.

15 It is of critical importance when converting natural shark cartilage to a finely divided purified state suitable for administration to a human or animal host in capsule, tablet, 20 suppository or powder form, that the protein and mucopolysaccharide factors of the shark cartilage not undergo denaturization. Should the activity of the protein factor of the shark cartilage undergo denaturization, the potency of the anti-angiogenesis activity of the natural shark cartilage will 25 be at least compromised and most likely destroyed. Excessive

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heat, above about 150°F can denature much of the protein content of the shark cartilage.

In accordance with the present invention, a low temperature method has been developed for converting natural shark cartilage into a substantially 100% pure, non-toxic, finely divided shark cartilage, free from adhering tissue, and without compromising the potency of the protein and mucopolysaccharide content of the natural unprocessed shark cartilage. Natural unprocessed shark cartilage comprises the fresh head, gill and spinal cartilage of the shark in its natural state.

The inventive process involves an initial step of physically removing adhering shark tissue from the natural unprocessed shark cartilage. This removal can be accomplished by hand, and also with the assistance of high-pressure water jets.

The initial removal of the shark tissue from the natural shark cartilage is followed by an enzymatic cleaning step using a suitable proteolytic enzyme such as Akalase[®] 2.4L (Novo Industries A/S, Denmark), or its equivalent. The enzyme treatment is best performed only after the amount of adherent shark tissue does not exceed about 3 to 5% by weight of the total shark cartilage and tissue.

The proteolytic enzyme is diluted in a ratio of about 1 part enzyme to about 1000 to 5000 parts water, and

preferably about 1 part enzyme to about 2500 parts water at a pH of about 7.0 to 9.5, and preferably a pH of about 8.5, and a temperature of about 20-30°C, preferably about 25°C, for about 30-70 minutes, preferably about 50 minutes. Visual inspection of the shark tissue during and after the enzyme treatment shows a marked deterioration of the tissue and its ability to adhere to the shark cartilage which facilitates its subsequent removal with a water spray or water jet treatment.

If visual inspection after the water spray treatment reveals residual shark tissue still adhering to the shark cartilage, any or all of the previous steps of removing the adhering shark tissue can be repeated until none or substantially no adherent tissue remains.

The shark cartilage is then chopped into particles having an average size of about $\frac{1}{4}$ inch. The reduction in particle size can be accomplished with a suitable shredder, such as a Franklin Miller Model 8000 Shredder (Franklin Miller, Inc., NJ), a heavy duty shearing device, having fixed and moving blades. Most importantly, the reduction in particle size of the shark cartilage at this stage is accomplished at ambient conditions, and the temperature of the shark cartilage undergoing size reduction should not exceed ambient temperature.

The chopped shark cartilage is then dried to a residual moisture content of about 6 to 10 weight % water,

preferably about 7-8 weight % water, and most preferably about 7.5 weight % water, at a temperature of about 100-140°F, and preferably below 110°F.

Following the initial size reduction, the shark cartilage is further reduced to a particle size of about 100 mesh (150 microns) to about 325 mesh (45 microns), and preferably about 200 mesh (75 microns). This additional particle size reduction operation is performed at conditions wherein the maximum temperature of the shark cartilage undergoing size reduction does not exceed 120°F.

The shark cartilage is preferably reduced to the desired particle size in a milling operation, such as the proprietary mechanized milling system at Powder Technology, Inc., Burnsville, MN, or equivalent, which uses a centrifugal mechanical milling system modified to provide a high shearing effect which cuts and grinds the shark cartilage to the desired particle size.

Controlled air volume and velocity through the system maintains low processing temperature and facilitates the size classification of the product. Temperature sensors are used to monitor the temperature of the shark cartilage during its size reduction to ensure that a maximum temperature of 120°F, and preferably 105°F is not exceeded.

Preferably, at least about 90% of the finely divided shark cartilage should pass through a 200 mesh screen for

maximum effectiveness. This particle size is finer than most talcum powders.

After the shark cartilage has been reduced to the desired particle size, it is then subjected to a conditioning operation to germinate any bacterial spores which may be present in the shark cartilage. This can be done by maintaining the finely divided shark cartilage at ambient relative humidity and a temperature of about 90 to 110°F, preferably about 100°F for about 24 to 36 hours, preferably about 30 hours.

The bacteria germinated from the spores are more susceptible to low temperature sterilization than the spores per se, which are significantly less susceptible to sterilization. Thus, bacteria contained in the shark cartilage in the spore state can survive a low temperature sterilization operation whereas the germinated bacteria are vulnerable to low temperature sterilization. Sterilization following conditioning can significantly reduce the bacteria counts.

The conditioned shark cartilage can be sterilized in a confined vessel or chamber at low temperatures on the order of about 120 to 140°F, preferably about 130°F, and an elevated pressure of about 26 pounds per square inch absolute (psia) for about 6 to 12 hours, preferably 8 to 10 hours in the presence of a sterilizing gas, such as ethylene oxide. The sterilizing

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gas is preferably a mixture of 12 volume % ethylene oxide and 88 volume % freon.

Prior to introducing the sterilizing gas into the chamber, steam can be introduced to bring the relative humidity to about 35 to 50% for about one hour. The steam is then removed, such as with an inert gas purge, and the sterilizing gas can then be introduced.

The extent of sterilization can be monitored by taking a sample of the shark cartilage and measuring the level of microorganisms to ensure the efficacy of sterilization through bacterial or microorganism reduction to a level of less than about 500 per gram, and preferably less than about 10 per gram in accordance with the procedure described in the FDA Bacteriological Analytical Manual, Chapter 4, pp. 4.01-4.04, 6th edition, 1984, which is incorporated by reference herein.

It is important to note that the low temperature gas sterilization treatment in the presence of a sterilizing gas, such as ethylene oxide does not adversely affect the activity and potency of the mucopolysaccharide and the protein factors in the shark cartilage.

It has been found that the low temperature conditioning and gas sterilization of the shark cartilage can be carried out conveniently by placing a specific amount of the finely divided shark cartilage in a paper or cellulosic enclosure having sufficient porosity to allow the sterilizing

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gas to permeate the enclosure and contact the finely divided shark cartilage for a time sufficient to sterilize it. The porosity of the enclosure is sufficient to confine the shark cartilage therein without allowing it to disperse or escape, and yet at the same time allow the sterilizing gas to penetrate and sterilize the shark cartilage.

The paper or cellulosic enclosure can also serve as packaging means for the sterilized finely divided shark cartilage product, which can then be stored or brought to a suitable facility for manufacturing tablets, capsules or suppositories from the finely divided shark cartilage.

It has been found that multi-walled, preferably 50 pound, triple walled, natural Kraft paper bags without plastic liners having a porosity of about 10 to 20 using the Gurley test method is preferred. The bag dimensions are about 15 inches x 3½ inches x 35 inches.

A predetermined amount, for example, twenty-five pounds of the finely divided shark cartilage can be placed in each bag after the milling operation. Each bag is then sealed. The sealed bags can then be placed flat in a cardboard box or gaylord and stacked, if desired, on a pallet. The cardboard boxes are preferably laminated 40 pound box weight corrugated paper with dimensions of about 35 inches x 35 inches x 35 inches. The bags containing the shark cartilage, lying flat, thereby allow the contents of the finely divided shark

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cartilage to settle therein to a thickness of about 3 inches, which is suitable for the conditioning and sterilization operations.

5 The porous paper or cellulosic enclosure, such as the triple-wall paper bag package is also a convenient means for the bulk packaging, and in situ conditioning and sterilization of any finely divided food grade or pharmaceutical material at low temperature. The finely divided food grade or pharmaceutical material can thereafter be stored or shipped to
10 another facility for further processing, and packaged for the trade or retail consumption.

After the sterilization step, a CAM (Chicken Chorioallantoic Membrane) assay procedure is used to measure angiogenesis inhibition of the sterilized shark cartilage. As
15 already noted, fertile chicken eggs are prepared for testing by either of two known procedures referred to in the art as the "window" or "egg culture" techniques. In each technique, the fertilized chicken eggs are maintained, typically in a humidified incubator at a temperature of about 36°C-37°C and in
20 a horizontal position with rotations twice daily.

In the window technique, an air pocket is created in the egg, often by withdrawing albumen, and several days after fertilization, such as the eighth day, a window of about 1.5 - 2.5 square centimeters is cut from the shell directly over the
25 air pocket. The underlying shell is carefully removed,

exposing a CAM that is undamaged and free from any shell or shell membrane fragments.

In the egg culture technique, fertile chicken eggs are incubated for three days, the shell is removed, and the embryo is placed into a petri dish without destroying the developing embryo. The embryos are then incubated for three more days, and a distinct CAM can be found around the embryo. A pellet made of agarose, containing the test material is then placed directly on the CAM.

After 24 hours of further incubation, a low-power microscope assessment is made of the possible changes in the CAM vascularization. A detailed description of this procedure is contained in U.S. Patent No. 5,075,112 to Lane. The amount of microscopic field where vascularization is inhibited, as well as the degree of inhibition, are estimated. A rating of 0 designates no effect, a rating of 1 designates a modest effect, and a rating of 2 indicates a marked effect. These ratings are based upon an average of 20 eggs per sample and comprise the "Vascularization Index" (VI).

The processing operations used to convert shark cartilage to a powdered state can materially effect the VI reading since improper processing methods can denature the active protein and mucopolysaccharide factors, and render the potency of the shark cartilage inactive. By following the aforementioned operations in processing the shark cartilage, VI

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readings of about 0.85 to about 1.1 can be achieved. VI readings of about 0.85 to 1.1 demonstrate that the active proteins have not been denatured. This compares favorably with a VI of 0.75 normally found with heparin/cortisone, which is usually considered to be the standard for the anti-angiogenesis test.

A typical chemical analysis of 100% pure unadulterated dry shark cartilage is approximately 45 to 55% mineral content, 30 to 40% protein, 6 to 9% carbohydrates, 5 to 8% water, and about 0.1 to 0.3% fat. The mineral content, including mineral salts, comprises about 60%, with calcium and phosphorus salts at a ratio of about 2 parts calcium to 1 part phosphorus.

Almost no heavy metals are found because the shark cartilage contains no blood vessels. Thus, the heavy metals often found in minimal amounts in shark meat do not exist in the shark cartilage. The high levels of calcium and phosphorus are the result of calcification of the cartilage, particularly the backbone cartilage.

Although the protein portion of the shark cartilage is diluted to some degree by the calcium, phosphorus, carbohydrate, and other natural components of the shark cartilage, these diluents are believed to play an active role in disease control. The mucopolysaccharides in the carbohydrates are believed to stimulate the immune system and

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work with the protein to fight diseases . The organic calcium and phosphorus content are used metabolically as nutrients.

The integrity and properties of the finely divided shark cartilage prepared in accordance with this invention can be retained in storage for up to about 2½ years.

In the following example, which is illustrative of the present invention, and throughout the patent application, all parts and percentages are by weight unless otherwise noted.

EXAMPLE

Sharks of the tiger and hammerhead species among others, are caught fresh in the Pacific Ocean and weigh an average of about 250 pounds each. The sharks are gutted and chilled with ice on fishing vessels. Equal amounts of head, gill and spinal cartilage are separated from the shark and further cleaned by hand to remove the adhering shark tissue from the raw shark cartilage in its natural state. Visual inspection of the shark tissue indicates that the amount of residual adhering shark tissue does not exceed about 3% to 5% by weight of the total shark cartilage and tissue. The initial removal of the shark tissue from the natural shark cartilage is followed by an enzymatic cleaning with Akalase™ 2.4L, a proteolytic enzyme diluted in a ratio of one part enzyme to 2,500 parts of water at a pH of 8.5 and a temperature of 25°C for 50 minutes.

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Visual examination of the shark tissue during and after the nzyme treatment shows a marked deterioration of the residual shark tissue and its ability to adhere to the shark cartilage. The remaining shark tissue is removed with a water spray treatment. At this point, visual observation reveals no more shark tissue adhering to the shark cartilage.

The shark cartilage is then chopped into particles having an average size of about $\frac{1}{4}$ inch with a Franklin Miller Model 8000 shredder. The shark cartilage is then dried to a residual moisture content of 10 weight % water at a temperature of 105°F.

Following the initial size reduction, the shark cartilage is further reduced to a particle size of about 200 mesh in a milling operation performed at Powder Technology, Inc., Burnsville, Minnesota under controlled temperature conditions wherein the temperature of the shark cartilage does not exceed 105°F during processing.

Twenty-five pound quantities of the shark cartilage are then placed in 50 pound triple-wall Kraft paper bags having a porosity of about 35 seconds per 300 cubic centimeters. The bags are then sealed and placed flat on pallets where the finely divided shark cartilage settles to an average thickness of about 3 inches.

The shark cartilage is then conditioned by maintaining it at a relative humidity of 0% for 30 hours at a

temperature of 100°F to germinate any bacterial spores that are present. The shark cartilage, still packaged in the paper bags with the germinated bacterial spores, is placed in a pressure controlled chamber and exposed to low-temperature sterilization using a sterilizing gas consisting of a mixture of 12 volume % ethylene oxide and 88 volume % freon introduced into the chamber at a temperature of 115°F and a pressure of 26 psia for 9 hours.

After the sterilization operation has been completed, samples of the sterilized shark cartilage are taken and tested in accordance with the procedure described in the FDA Bacteriological Analytical Manual, Chapter 4, pages 4.01-4.04, (6th edition, 1984), to determine the microorganism count, which averages about 5 per gram. A CAM assay gives a reading of 1.0. The bagged shark cartilage is then shipped to a manufacturing facility for encapsulating the shark cartilage into 750 mg capsules for the retail trade.

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What is claimed is:

Claim 1. A low temperature method for producing a 100% pure non-toxic, finely divided shark cartilage from natural shark cartilage, free from adhering tissue, and without denaturing the protein activity or degrading the inherent nutritional content of said natural shark cartilage, comprising:

(a) physically removing the shark tissue from the natural shark cartilage by means selected from the group consisting of hand cleaning, cleaning with water jets, and combinations thereof, until the amount of adherent shark tissue does not exceed about 3 to 5% by weight;

(b) contacting the natural shark cartilage with a proteolytic enzyme for about 30 to 70 minutes to further loosen or remove residual shark tissue adhering to the shark cartilage;

(c) chopping the shark cartilage into particles having an average size of about $\frac{1}{4}$ inch;

(d) drying the shark cartilage to a residual moisture content of about 6 to 10% H_2O at a temperature of about 110° to 140°F;

(e) further reducing the particle size of the shark cartilage to about 100 to 325 mesh at a temperature below 120° F;

(f) conditioning the shark cartilage to
25 germinate any bacterial spores present therein by maintaining
said cartilage at a relative humidity of about 0 to 30% and
temperature of about 90° to 120°F for about 24 to 36 hours; and
(g) sterilizing the shark cartilage in the
presence of a sterilizing gas at a temperature below 150°F
30 until the microorganism count is reduced to below about 500 per
gram.

Claim 2. The method of Claim 1, wherein the shark
cartilage has a CAM assay of at least about 0.85.

Claim 3. The method of Claim 1, wherein the
proteolytic enzyme used in step (b) is diluted to a ratio of
about 1 part enzyme to about 1,000 to 5,000 parts water.

Claim 4. The method of Claim 1, wherein the shark
cartilage is reduced to a particle size in step (g) of about
200 mesh.

Claim 5. The method of claim 1, wherein prior to
the conditioning step (f), the shark cartilage is placed in
predetermined amounts in a porous enclosure whose porosity is
sufficient to allow a sterilizing gas to penetrate the
5 enclosure and sterilize the shark cartilage.

Claim 6. The method of claim 5, wherein the porous enclosure is selected from the group consisting of paper and cellulose.

Claim 7. The method of Claim 1, wherein the pure dried shark cartilage has the following analysis:

minerals:	45% to 55%
protein:	30% to 40%
carbohydrates:	6% to 9%
moisture:	5% to 8%
fat:	0.1% to 0.3%.

Claim 8. The method of Claim 1, wherein the sterilizing gas is ethylene oxide.

Claim 9. A method for low temperature gas sterilization of a finely divided food grade or pharmaceutical product, comprising placing a predetermined amount of the finely divided food grade or pharmaceutical product in a porous enclosure wherein the porosity of said enclosure is sufficient to prevent the finely divided food grade product from escaping through the pores of the enclosure and still allow a low temperature sterilizing gas to penetrate the enclosure and contact the finely divided food grade or pharmaceutical product for a time sufficient to sterilize it.

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claim 10. The method of claim 9, wherein the porous enclosure comprises a paper or cellulosic product.

INTERNATIONAL SEARCH REPORT

International application No.
PC/US93/10764

A. CLASSIFICATION OF SUBJECT MATTER

IPC(S) : C07G 17/00

US CL : 424/548; 435/262, 267

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/548; 435/262, 267

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS/CA/BIOSIS/MEDLINE/EMBASE/WPI/BIOTECH ABS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	US, A, 5,075,112 (LANE) 24 DECEMBER 1991, SEE ENTIRE DOCUMENT.	1-10
Y	US, A, 4,350,682 (BALASSA) 21 SEPTEMBER 1982, SEE ENTIRE DOCUMENT.	1-10
Y	WO, A, 80/02501 (BALASSA) 27 NOVEMBER 1980, SEE ENTIRE DOCUMENT.	1-10
Y	US, A, 4,060,081 (YANNAS ET AL) 29 NOVEMBER 1977, SEE ENTIRE DOCUMENT.	1-10
Y	US, A, 4,656,137 (BALASSA) 07 APRIL 1987, SEE ENTIRE DOCUMENT.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Authorized officer

JEFFREY J SEVIGNY

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